

**Follow-up of patients with
early breast cancer:
a systematic review**

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Follow-up of patients with early breast cancer: a systematic review
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EXECUTIVE SUMMARY

There have been a number of proposed advantages for follow-up care after treatment for early breast cancer, including early detection of a recurrence or new primary breast cancer, monitoring of treatment-related toxicities and provision of psychosocial support. Previous clinical practice guidelines from National Breast Cancer Centre (NBCC)* were published in 2001 which included information on follow-up care after treatment of breast cancer. National Breast and Ovarian Cancer Centre (NBOCC) undertook a systematic review of literature published between January 2000 and January 2008 to update these guidelines. Many papers have been published on this topic during this time however a limited number of studies were identified that were considered high quality evidence, such as randomised controlled trials.

The review considered eleven clinical practice guidelines, eight systematic reviews, five randomised trials (RCTs), seven comparative studies, 17 observational studies, five prognostic studies and 18 qualitative studies. Information was identified for the following topics:

- method of detection of recurrence and/or contralateral breast cancer
- clinical vs. intensive follow-up
- interval/frequency of follow-up
- provider of follow-up care
- shared care
- psychosocial/Quality of Life (QoL) aspects – including patient/physician perceptions of follow-up care, patient needs, patient preferences
- cost/economics of follow-up care.

The systematic review found that physical examination, personal history and mammography were regularly performed in follow-up care after treatment for breast cancer. Routine use of intensive methods of follow-up (e.g. blood tests, chest x-ray etc) did not improve patient outcomes. The person providing the follow-up care does not appear to influence survival or quality of life outcomes. Patients' needs during follow-up care will vary and should be discussed during routine visits. Further clinical trial information is needed to determine optimal interval and duration of follow-up visits.

* In February 2008 National Breast Cancer Centre, incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

1 Background

National Breast Cancer Centre (NBCC)* released the *Clinical Practice Guidelines: Management of Early Breast Cancer* in 2001,¹ which includes a chapter discussing follow-up care after breast cancer treatment. The guideline considered all aspects of follow-up, including the goals of follow-up, the economics of follow-up, who should be providing follow-up care, and gave a recommended follow-up schedule (see Table 1).

The proposed advantages of follow-up care after breast cancer treatment included:

- the early detection of local recurrence
- screening for a new primary breast cancer
- detection of treatment-related toxicities
- provision of psychosocial support
- identification and review of family history.

Table 1 NBCC clinical practice guideline recommendations 2001¹

NBCC Recommended follow-up schedule			
	1-2 Years	3-5 Years	After 5 Years
History & Exam	Every 3 months	Every 6 months	Every year
Mammography (& ultrasound if indicated)	At 6-12 months after radiotherapy for conserved breast	Every year	Every year
Chest X-ray		Only if clinically indicated	
Bone Scan, blood count & biochemistry		Only if clinically indicated	

*Not every clinician involved in the care of a woman will be closely involved in her follow-up.

*Symptoms should be assessed as they arise.

A single guideline recommendation was made in the 2001 guidelines regarding follow-up:

“A minimal follow-up schedule is recommended; as there is no evidence that frequent intensive follow-up confers any survival benefit or increase in quality of life”.

This recommendation was based on level II evidence (NHMRC Levels of Evidence,² Appendix 1) from two papers.^{3, 4}

A recent appraisal of guideline development processes at NBOCC identified a need to produce timely, topic specific guideline recommendations in key areas of changing evidence. The need to review the evidence and update guidelines on the appropriate follow-up of women following treatment for early breast cancer has been identified. The purpose of this review was to identify evidence published since 2000 on follow-up care for women after breast cancer treatment to update the 2001 guidelines. Different methods and models of follow-up care will be reviewed.

* In February 2008 National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

2 Methods

The objective of the review is to investigate follow-up procedures for women who have completed active treatment for early breast cancer.

Research questions addressed in this systematic review are:

- Does the method of detection of a recurrence (patient, GP, mammogram) influence outcomes?
- Does intensive follow-up provide benefits over standard follow-up?
- What is the optimal interval and duration of follow-up care?
- Does the person who provides follow-up care influence outcomes?
- Do shared care models of follow-up influence outcomes?
- What are the patient's preferences for follow-up models of care?
- What evidence surrounds the role of follow-up care in psychosocial outcomes of women?
- Are there subsets of the defined population who have specific follow-up requirements?
- Economics of follow-up

2.1 Inclusion criteria

2.1.1 Participants

Women/patients who have completed active treatment (surgery, radiotherapy and/or chemotherapy) for early breast cancer.

2.1.2 Intervention

Routine follow-up care for the purpose of detecting recurrence and/or new primary cancer, monitoring side effects of treatment and providing psychosocial care.

Standard follow-up procedures include personal history, physical examination and mammography. Additional tests may be performed where clinically indicated. Standard follow-up may also be referred to as clinical, routine or minimal follow-up.

Intensive follow-up procedures include routine use of blood tests, x-rays and bone scans.

2.1.3 Comparison

Any comparisons of different kinds of follow-up care were recorded including:

- comparisons of methods for detection of recurrence/contralateral breast cancer (CBC) – e.g. asymptomatic vs. symptomatic; physical examination vs. mammography
- provider of follow-up care – e.g. specialist, general practitioner (GP), nurse
- standard vs. intensive follow-up
- different frequency or duration of follow-up.

2.1.4 Outcome measures

The types of outcome measures were:

- overall survival
- disease-free survival
- detection of recurrence/CBC
- treatment given
- QoL
- patient/physician preferences.

2.2 Literature search

A systematic literature search was conducted in January 2008 to identify relevant trials which addressed the inclusion criteria. The search was conducted over several databases/sources (see Appendix 2), including:

- Medline (Ovid)
- EMBASE
- Pubmed
- CINAHL
- PsycINFO
- Cochrane Library, Issue 1 2008.

In addition to the above databases, guidelines and health technology assessment websites were searched for relevant information.

A list of the guidelines, clinical trials and health technology assessment websites searched can be found at Appendix 3.

Additional papers identified from personal files and the reference lists of included papers were also sourced.

The search strategy used combined key terms which described breast cancer, and follow-up/surveillance (see Appendix 4). The search was limited to trials conducted in humans which were published from January 2000 – January 2008 in the English language.

After the removal of duplicate citations and the addition of further citations sourced, a total of 3607 unique citations remained. The titles and abstracts of these citations were assessed by two independent reviewers to determine eligibility for the current review based on the criteria described above. Ineligible studies were classified using the exclusion criteria below. For citations which provided insufficient information to assess eligibility, the full text was retrieved for assessment, by the same two independent reviewers.

2.2.1 Exclusion Criteria

Papers were excluded if they met any of the following criteria:

- not original clinical study — publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters
- inappropriate population — studies conducted in a population other than patients treated for early breast cancer. Studies that were conducted in a general cancer population were included only if data on breast cancer patients were reported separately
- inappropriate intervention — studies not investigating follow-up as defined in the inclusion criteria. Studies investigating diagnostic follow-up procedures (e.g. use of MRI or PET after clinical suspicion of recurrence) were not included
- inappropriate outcomes – studies not reporting on the effect of follow-up. Studies investigating patterns of care/receipt of surveillance were not included
- not published in the English language.

Based on these criteria, 3384 articles were excluded. The full text of the remaining 223 citations were retrieved and assessed to identify which met the inclusion criteria for the review. After full text assessment 73 citations were identified as eligible for the current review (see Appendix 5). Of the included citations, there were 11 guideline recommendations, five randomised controlled trials which addressed provider of follow-up care and standard vs. intensive follow-up, the remaining papers were comparative (cohort or case-control) trials, and observational or qualitative studies.

2.3 Data extraction

Data extraction was performed independently by two reviewers. Where multiple citations existed for one trial, data was extracted from the latest available publication, however if additional information of interest was reported in a previous publication this was also included. Descriptive data extracted from the studies included characteristics such as population, interventions and primary outcomes.

Outcome data extracted from the studies included overall survival, disease-free survival, QoL and detection of recurrence or CBC.

Qualitative data was recorded separately, with key themes and findings reported rather than specific outcomes.

3 Results

3.1 International guidelines

Various international guidelines were identified either through the literature search or from health technology assessment and guidelines websites. Many guidelines on the use of follow-up for breast cancer patients were identified however they are limited to general guidance. The guidelines recommend regular physical examinations and mammography be performed. There are no clear guidelines on how frequently follow-up should occur or for how long it should continue after initial diagnosis. The guidelines acknowledge a lack of definitive evidence in the published literature. Intensive surveillance, for example using tumour markers or positron emission tomography (PET), is not recommended by any group.

3.1.1 National Cancer Control Network (NCCN) 2008⁵

NCCN in the United States updated their breast cancer guidelines in 2008. The surveillance/follow-up section recommends the following:

- interval history and physical examination every 4–6 months for 5 years then every 12 months
- mammogram every 12 months (and 6–12 months post-radiation therapy if breast conserved)
- for women on tamoxifen: annual gynecologic assessment every 12 months if uterus present
- for women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health
- assess and encourage adherence to adjuvant endocrine therapy.

3.1.2 Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) 2007⁶

AGO in Germany updated their 2002 recommendations for the diagnostic and therapy of breast cancer in 2007.⁶ The updated recommendations for follow-up were:

- AGO advises against surveillance by imaging including PET for screening or detection of metastases
- to speak intensively with each patient about complaints in the interval since the last visit, to thoroughly perform clinical examination and to prescribe mammography of the affected breast every 6 months (contralateral every 12 months) in order to detect potential curable locoregional recurrences or secondary cancers.

3.1.3 American Society of Clinical Oncology 2006⁷

In 2006, ASCO updated the breast cancer follow-up and management guidelines in the adjuvant setting. The update was based on evidence up to March 2006, the updated guidelines conclude that “careful history taking, physical examination, and regular mammography are recommended for appropriate detection of breast cancer recurrence”. Pelvic examination is also recommended, particularly for women on tamoxifen, to detect endometrial cancer. ASCO also had guidelines on tumour markers in breast cancer (BC)⁸ (none are recommended for surveillance) and monitoring cardiac and pulmonary side effects in cancer patients.⁹

3.1.4 Health Canada 2005^{10, 11}

In 1998 Health Canada produced guidelines for the care and treatment of breast cancer, including follow-up after treatment; these guidelines were updated in 2005. The guidelines now recommend:

- all patients with breast cancer should have regular follow-up surveillance
- the frequency of visits should be adjusted according to individual patients needs
- all visits should include a medical history. Physical examination should include breasts, regional lymph nodes, chest wall, lungs and abdomen. The arms should be examined for lymphoedema. Annual visits should include mammographic examination
- routine laboratory and radiographic investigations should not be carried out for the purpose of detecting distant metastases
- patients should be encouraged to report new, persistent symptoms promptly, without waiting for the next scheduled appointment
- if a women wishes to carry out a breast self examination, it is reasonable to teach her the proper procedure
- psychosocial support should be encouraged and facilitated
- participation in clinical trials should be encouraged and facilitated
- the responsibility for follow-up should be formally allocated to a single physician
- communication between all members of the team must be ensured to avoid duplication of visits and tests.

3.1.5 Scottish Intercollegiate Guidelines Network (SIGN) 2005¹²

SIGN published management of breast cancer guidelines in 2005. The follow-up guidelines recommend:

- clinical examination is the best method for detecting recurrence in the chest wall or axilla
- mammography should be used to detect recurrence in patients who have undergone previous treatment for breast cancer
- routine diagnostic tests to screen for distant metastases in asymptomatic women should not be performed
- patients and primary care teams should have procedures in place for prompt re-referral to a person with responsibility for follow-up and access to support services. They should be encouraged to report new, persistent symptoms promptly without waiting for the next scheduled appointment
- patients with breast cancer should have access to input from a specialist palliative care team.

3.1.6 Association of Breast Surgery 2005¹³

The Association of Breast Surgery in the United Kingdom (UK) published guidelines in 2005. The guidelines address the management of symptomatic breast disease. For clinical follow-up the guidelines recommend:

- patients on continuing active treatment may be followed up until such treatment has been completed
- high risk patients may be followed up more closely with joint care by surgeons and oncologists according to agreed local protocols

- data about long term follow-up is essential in monitoring clinical outcomes
- discharge of follow-up to primary care should be an agreed and integrated process and subject to audit
- if a GP detects a possible recurrence the patient should be referred back to the breast unit
- patients diagnosed and treated for breast cancer will have ongoing requirements to meet their psychosocial needs, surveillance of ongoing treatment effects, monitoring of primary treatment morbidity and monitoring of recurrence rates.

3.1.7 European Society of Medical Oncology (ESMO) 2005¹⁴

In 2005 ESMO updated their 2001¹⁵ guidelines.[†] The updated conclusions were:

- history taking, eliciting of symptoms and physical examination every 3–6 months for 3 years, every 6–12 months for 3 years, then annually with attention paid to long-term side effects
- ipsilateral (after breast conserving surgery) and contralateral mammography every 1–2 years
- not routinely recommended for asymptomatic patients: blood counts, chemistry, chest x-rays, bone scan, liver ultrasound, computed tomography (CT) scans of chest and abdomen, and any tumour markers.

3.1.8 Royal College of Radiologists 2003¹⁶

The Royal College of Radiologists in the UK developed guidelines on screening and symptomatic breast imaging in 2003. These guidelines state:

- clear evidence on the frequency of follow-up mammography is not available but it is considered reasonable practice that it should be at least once every 2 years and no more frequent than annually
- routine imaging investigation should be restricted to those where the presence of metastasis will alter patient management.

3.1.9 National Institute for Clinical Excellence (NICE) 2002¹⁷

NICE in the UK recommend that guidelines for limited (two or three years) follow-up should be agreed by each network. Routine long-term follow-up is not recommended. Intensive follow-up is also not recommended.

[†] In May 2008 (after review was completed) ESMO published updated guidelines however the follow-up recommendations remained unchanged.

Table 2 International follow-up guidelines

Guidelines	Follow-up components				
	Mammography (general)	Mammography (post conserving therapy)	Clinical Visit (History & physical exam)	Self-breast examination (BSE)	Intensive follow-up
NCCN 2008		Every 12mths (and 6-12mth post-radiation therapy)	Every 4-6mths for 5yrs, then every 12mths		
AGO 2007		Every 6mths (every 12mths for contralateral breast)			Not recommended
ASCO 2006	Annually	Approx 6mths after radiotherapy, then every 6-12mths, then annually if stability of mammographic findings is achieved after locoregional therapy	every 3-6mths for first 3yrs after primary therapy; every 6-12mths for years 4 and 5; then annually	All women should be counselled to perform monthly BSE	Not recommended
Health Canada 2005		Annual visits	All visits should include a medical history. Physical exam should include breasts, regional lymph nodes, chest wall, lungs and abdomen	If a women wishes to carry out BSE it is reasonable to teach her the proper procedure	
SIGN 2005	One to twice yearly within 1 st five years				Not recommended
Association of Breast Surgery, 2005	Every 1-2yrs for up to 10yrs after diagnosis		Followed for five years (frequency not stated)		
ESMO 2005		Ipsilateral and contralateral every 1-2yrs	Every 3-6mths for 3yrs, every 6-12mths for 3yrs, then annually		Not recommended
NICE 2002					Not recommended
Royal College of Radiologists, 2003	Every 3yrs	At least every 2yrs, no more than every year			

Note: BSE= breast self examination; mths=months; yrs=years

3.2 Systematic reviews

Eight systematic reviews on follow-up care of breast cancer patients were identified. Some of the reviews identified included RCTs only^{18, 19} however others included information from all levels of evidence. Overall the reviews found limited definitive information on follow-up procedures. Although these reviews have been published after 2000, most included papers published prior to 2000. Where relevant, the included papers published after 2000 have been sourced and included in the current NBOCC review and reported on individually.

3.2.1 Sheppard 2007²⁰

This literature review includes information from 1989 to January 2006. Overall no evidence was found to suggest routine clinical follow-up improves patient's survival outcomes. Nurse-led and GP follow-up were demonstrated as comparable to hospital-based consultant-led care for detection of disease and psychological outcomes. Limited information was available on QoL of patients.

3.2.2 Montgomery 2007a,¹⁸ b²¹

*Alternative methods of follow-up (a)*¹⁸

This review included RCTs comparing routine clinical and mammographic follow-up with an alternative, or comparing different frequencies or durations of clinical follow-up. The review found there were no RCTs with sufficient power to recommend an acceptable frequency or duration of follow-up. No RCTs confirm the safety of alternative methods of follow-up.

*Routine clinical examination (b)*²¹

Review of 12 papers found that 30–40% of potentially treatable relapses are detected by patient self-examination. In studies published after 2000, 40% of treatable relapses are detected by mammography and 15% are detected on routine clinical examination. The review states that there is no evidence to suggest that clinical examination confers a survival advantage compared with other methods of detection.

3.2.3 de Bock 2004²²

A meta-analysis of 12 studies including 5045 patients reported 40% of isolated locoregional recurrences diagnosed during routine visits or routine tests without symptoms. Of these 47% were diagnosed after mastectomy, 36% after breast conserving therapy (BCT). In addition, 18% of locoregional recurrences were diagnosed during routine visits with symptoms and 41% were diagnosed outside of routine visits. The method of detection of recurrence (e.g. physical exam, mammography) was not assessed.

3.2.4 Cochrane review 2004¹⁹

A Cochrane review (published in 2000 and updated in 2004) included data from four RCTs, one on specialist follow-up vs. GP follow-up, one on conventional follow-up vs. follow-up limited to time of mammography but with on-demand consultation available and two on clinical vs. intensive follow-up. The four trials in this review were all published prior to 2000. A meta-analysis of the two papers

comparing intensity of follow-up found no difference in overall mortality between non-intensive and intensive follow-up strategies (OR:0.96; 95% CI: 0.80, 1.15; p=0.7). Similar results were found for disease-free survival (OR: 0.84; 95% CI:0.71, 1.00; p=0.05). The paper comparing specialist to GP follow-up found no significant differences in time to detection of recurrence or QoL, however patient satisfaction was higher in patients treated by the GP. The paper on conventional vs. limited follow-up found no significant differences between the groups for telephone use or frequency of GP consultations.¹⁹

3.2.5 Older reviews

Collins *et al* (2004)²³ reviewed 38 papers published 1989 – 2001 from which, few definitions and/or guidelines on optimal services for follow-up care could be identified. Collins *et al* did report that intensity of follow-up or location of care did not affect patient survival or quality of life and that patients held positive attitudes towards follow-up, although psychological distress was consistently high regardless of location of services.

Grunfeld *et al* (2002)²⁴ reported a systematic review of 15 papers on surveillance mammography, all published prior to 2000. Method of detection of ipsilateral recurrence (mammography alone, physical examination alone, or combination) did not influence overall survival (OS) or disease free survival (DFS).

Barnsley *et al*²⁵ reported on surveillance mammography following breast reconstruction in 2007 however only one included paper was published after 2000. The paper concludes that certain local recurrences are able to be detected by surveillance mammography but that there is a paucity of evidence on this issue.

3.3 Included studies

Included papers were assessed and sorted into different categories/research questions, some of these categories were pre-defined prior to the literature search, however others arose based on the information identified during the literature search:

- method of detection of recurrence and/or contralateral breast cancer
- standard vs. intensive follow-up
- interval/frequency of follow-up
- provider of follow-up care
- shared care
- psychosocial/QoL – patient/physician* perceptions of follow-up care,* patient needs,* patient preferences
- subgroups
- cost/economics.

* additional topics identified after search

Limited high-quality information (e.g. RCTs) was available on follow-up care after breast cancer, the few RCTs identified compared different providers of follow-up care and standard vs. intensive follow-up. Much of the information on follow-up care was from comparative (cohort or case-control) and

observational studies however some information was available from qualitative research such as surveys/questionnaires, focus groups and interviews.

Outcomes of papers varied, many focused on detection of recurrence, others focused on QoL outcomes. Limited information was available on OS and DFS outcomes.

3.3.1 Follow-up tests

- ***Does the method of detection of a recurrence (patient, GP, mammogram) influence outcomes?***

Description of studies

Originally the research question for this section was to investigate whether the person detecting the recurrence influenced outcomes. However as information was available on particular methods of detection of recurrence (e.g. mammography, clinical examination), the question was broadened to include any reported difference in outcomes based on any method of detecting a recurrence (or CBC). This section includes papers comparing patients who were asymptomatic or symptomatic when a recurrence was detected, papers comparing different methods of detection (mammography, clinical examination), or papers which reported detection rates of specific methods such as mammography (considered a standard method of detection) or tumour markers (considered an intensive method of detection).

Outcomes

Asymptomatic vs. Symptomatic

Four papers particularly compared patients who were asymptomatic at time of detection of recurrence compared to those who presented with a recurrence symptomatically. The follow-up schedule differed between trials. The study by Perrone[‡] performed intensive surveillance,²⁶ while the remaining trials utilized standard follow-up protocols, see Table 3.

The percentages of patients with a recurrence being asymptomatic at time of detection varied between trials from 9%²⁸ to 52%.²⁶

[‡] Perrone has been excluded from NBOCC's follow-up clinical practice guideline as the data presented was not strong enough. Weaknesses of the study included: no control group, original treatment received by patients prior to follow up was not indicated, no indication of status of recurrence i.e. slow growing versus aggressive, age and nodal status was not used in the analysis.

Table 3 Study characteristics of trials comparing asymptomatic vs symptomatic recurrence

Trial	Physical exam	Mammography	Other tests
Perrone 2004 ²⁶	Every 3mths for 1 st 3yrs; every 6 months 4 th & 5 th yrs; once a year for another 5yrs	Every 2 yrs	Blood tests every 3mths for 1 st 3yrs; every 6mths 4 th & 5 th yrs; once a year for another 5yrs X-ray & bone scintigraphy & liver echography – variable on basis of different risk of relapse
Te Boekhorst 2001 ²⁷	& history every 3mths for 1 st 2yrs; every 6mths 3 rd – 5 th yrs; every year thereafter	Every year	Additional diagnostic tests only if symptoms suggestive of recurrence Early years of study performed chest radiographs, bone scintigrams and lab tests routinely.
Donnelly 2001 ²⁸	Not defined – no set protocol for follow-up – based on BASO guidelines		
Hiramanek 2004 ²⁹	No set protocol - generally every 6mths for 1 st 2yrs, then annually to five years	Every year	Not routinely undertaken

Note: mths=months; yrs=years

Stage of disease detected

Patients who were asymptomatic were more likely to be diagnosed with local recurrences compared to symptomatic patients who were more likely to present with distant recurrence, see Table 4.²⁶⁻²⁹

Table 4 Location of asymptomatic vs. symptomatic recurrence

Trial	Group	Recurrence			CBC
		Local/locoregional	Distant	Locoregional + distant	
Perrone 2004 ²⁶	Asymptomatic n=110 (52%)	72 (65%)	32 (29%)	6 (5%)	
	Symptomatic n=101 (48%)	32 (31%)	66 (65%)	3 (2%)	
te Boekhorst 2001 ²⁷	Asymptomatic n=100 (37%)	45%	47%	8%	
	Symptomatic n=170 (63%)	14%	78%	8%	
Hiramanek 2004 ²⁹	Asymptomatic n=7 (17%)	57%	29%	-	14%
	Symptomatic n=31 (74%)	16%	74%		10%
Donnelly 2001 ²⁸	Asymptomatic n=9 (9%)	100%			
	Symptomatic n=95 (91%)	29%	71%		

Rates of detection by different methods

In the study by Perrone *et al*,²⁶ 52% of the reported recurrences were asymptomatic. Of the asymptomatic recurrences 59% were detected by clinical examination (the majority [91%] of these were local recurrences). Twenty-eight of the 110 asymptomatic recurrences were detectable by

CA15-3 tumour marker levels with a median lead time (interval from first positive marker to verification of recurrent disease) of 104 days.

The te Boekhorst study²⁷ reported that 54% of the asymptomatic recurrences were detected by physical examination, 12% were detected by mammography. Common complaints in the symptomatic group included bone pain (44%), shortness of breath (15%), palpable lesions (12%) or enlarged lymph node (12%).

Seven of the nine asymptomatic recurrences in the Donnelly study²⁸ were detected by clinical examination, the remaining two were detected by surveillance imaging.

Hiramanek²⁹ presented data from a retrospective review of 42 patients who had a recurrence. Patient symptoms were reported as the first indicator of recurrence in 31 cases (74%). Follow-up examination detected two recurrences (5%), routine mammogram detected five (12%) and 10% were unknown.

Overall survival

Overall survival was reported in two papers, see Table 5. Perrone *et al*²⁶ reported a significantly longer median survival estimate for asymptomatic cases compared to symptomatic cases (101 vs. 65 months; $p < 0.001$).

In the study by te Boekhorst *et al*²⁷ the overall 5-year survival for all recurrences (locoregional and distant) was better in the asymptomatic group than the symptomatic group (62% vs. 46%; $p = 0.0003$), however, when locoregional and distant recurrences were analysed separately the difference was not apparent (locoregional: 78% vs. 61%, $p = 0.34$; distant: 55% vs. 46%, $p = 0.13$).

Disease-free survival

While Perrone *et al*²⁶ reported a shorter relapse-free interval in symptomatic cases compared to asymptomatic cases (28 vs. 35 months), due to the limited sample size this was not statistically significant.

The te Boekhorst study reported no significant differences in DFS between the asymptomatic or symptomatic groups (median disease free interval: 28 vs. 25 months).²⁷

Table 5 Survival outcomes for asymptomatic vs symptomatic recurrence

Study	Group	Overall survival		Disease-free survival	
Perrone 2004 ²⁶	Asymptomatic n=110	Events: 80; Median: 101mths	$p < 0.001$	Median: 35mths	Not significant
	Symptomatic n=101	Events: 87; Median: 65mths		Median: 28mths	
te Boekhorst 2001 ²⁷	Asymptomatic n=100	All: 5yr 62% Locoregional: 5yr 78% Distant: 5yr 55%	All: $p = 0.0003$; Locoregional: $p = 0.34$; Distant: $p = 0.13$	Median: 28mths	Not significant
	Symptomatic n=170	All: 5yr 46% Locoregional: 5yr 61% Distant: 5yr 46%		Median: 25mths	

Note: mths=months; yrs=years

Interval presentation

Most patients who are symptomatic present at interval visits however some patients wait to attend routine follow-up visits to discuss symptoms. Donnelly *et al* (2001)²⁸ reported that of 104 patients with recurrent disease, 77 (74%) presented at interval appointments when they became symptomatic. Of the remaining 27 patients, 18 had symptoms when they attended the routine clinic visit. The median duration of symptoms before attending clinic was one month for routine reviews and three weeks for interval referrals.

Hiramanek²⁹ reported that overall 76% of recurrences were presented at unscheduled appointments (of which 53% were self-referred by patient). Of the 31 patients who were symptomatic, 27 attended unscheduled visits and four attended scheduled visits. Five recurrences were detected in unscheduled visits in patients who were asymptomatic.

Other papers identified in the review also reported some information on interval presentation. Grogan *et al*³⁰ report that 71% of total recurrences presented at an interval visit. However not all trials report such high rates of interval presentation, Montgomery *et al* (2007c),³¹ and Churn & Kelly³² reported only 21% and 36% of patients had their relapse detected at an interval appointment respectively.

Specific methods of detection

Different methods used to detect recurrence using a clinical follow-up schedule include, mammography, clinical examination/palpation, self-detection (symptomatic), and occasionally ultrasonography. Some studies were identified that reported which particular method detected a recurrence. Reports varied in the definition of recurrence; details on how relapses were detected are listed in Table 6, stratified by how recurrence was defined in trials. The number of recurrences detected by each method varied greatly between the trials.

An abstract presented at SABCS³³ reported that 8% of parenchymal recurrences and 53% of non-parenchymal recurrences were detected by the clinician only and that 19% of relapses would have been missed if routine clinical follow-up after BCT was not performed.

Stage of disease

A study on the detection of CBC found that 83% of CBCs detected by mammography alone had good/excellent prognostic characteristics compared to 38% of CBCs detected by clinical examination at routine appointments and 40% for CBCs detected at interval appointments.³⁴

Montgomery *et al* reported that in patients with an ipsilateral breast recurrence, there was no significant difference in any of the clinicopathological features in relation to how relapse was detected.³¹

Overall survival

Doyle⁴⁰ found the method of detection of local recurrence predicted OS at 5-years after recurrence, for patients with local recurrence detected by physical examination the 5-year OS was 73%

compared with 91% for those with recurrence detected by mammography and 93% for those detected by both (p=0.04).

A univariate analysis by Robinson *et al*⁸⁹ found that survival was significantly associated with method of detection of CBC in both younger (<40 years) and older (55-59 years) patients. The 10 year survival rate for patients with CBC detected by mammography was 78% for younger patients and 62% for older patients compared with 64% for younger patients and 25% for older patients with CBCs detected clinically. In this study clinical detection included physical examination or symptomatic disease and some younger patients had ultrasonography in addition to mammography.

Kaas *et al*¹ report that patients with CBC detected by mammography had better breast cancer-specific survival than those whose CBC was detected by clinical examination (p=0.015).

Montgomery *et al* reported that in patients with an ipsilateral breast recurrence, overall survival was reduced in those where the recurrence was detected clinically (p=0.0002) however there was no association between method of detection of a new contralateral breast cancer and survival.³¹

Disease-free survival

A Hong Kong study of surveillance mammography after BCT found there was no difference in disease free survival between patients with ipsilateral breast cancer recurrence detected by surveillance mammography or ultrasonography compared to patients with their recurrence detected by symptoms or palpation (p=0.342).³⁷

Specific methods of intensive follow-up

Information was available from five trials on the use of tumour markers as part of an intensive follow-up schedule.⁴²⁻⁴⁶ Overall, tumour markers have a low sensitivity but a high specificity for detection of recurrence of breast cancer, see Table 7. Using a combination of markers increases the sensitivity of the test(s).⁴⁵

The mean lead times for the tumour markers varied, Nakamura *et al*⁴⁴ reported 334 days for CEA and 211 days for CA 15-3. Kokko *et al*⁴³ reported 89 days for CA 15-3. Nicolini *et al*⁴⁵ reported a wide range for the various tumour markers and combinations from 60 to 219 days. Perrone²⁶ reported a median lead time of 104 days for CA 15-3.

Table 6 Method of detection of recurrence/contralateral breast cancer

Study	Patient numbers (total relapses)	Number of patients with specific relapses	Patient detected relapses	Mammogram detected relapses	Clinical examination detected relapses	Ultrasound detected relapses
Local recurrence						
Grogan 2002 ³⁰	438 (21)	3	1 (33%)	2 (66%)		
Ashkanani 2001 ³⁵	695 (21)	21 [^] (3%)		10 (48%)	11 (52%)	
Regional recurrence						
Grogan 2002 ³⁰	438 (21)	6*(6%)	5 (83%)		1 (17%)	
Locoregional recurrences						
Montgomery 2007c ^{†31}	1312 (108)		37 (34%)	56 (54%)	15 (14%)	
Distant metastases						
Grogan 2002 ³⁰	438 (21)	12 (12%)	11 (92%)	1 (8%)		
Ipsilateral recurrence						
Chen 2003 ³⁶	(196)	125 (64%)		79 (63%) [48 (38%) detected by mammogram only] 31 (25%) detected by both mammogram + clinical exam	77 (62%) [46 (37%) detected by clinical exam only]	
Yau 2007 ³⁷	511(36)	23 (4.5%)	2 (9%)	10 (43%)	8 (35%)	3 (13%)
Montgomery 2007c ^{€31}	1312 (108)	71	29 (41%)	29 (41%)	13 (18%)	
Contralateral breast cancer						
Kollias 2000 ³⁴	2511 (65)	65 (2.6%)	20 (31%)	24 (37%)	21 (32%)	
Kollias 2000 ³⁴ – <50	(21)		11 (52%)	8 (38%)	2 (10%)	
Kollias 2000 ³⁴ – ≥50	(44)		9 (20%)	13 (30%)	22 (50%)	
Johnson 2000 ³⁸	216 (17)	17~(8.3%)	8	5	4 [‡]	
Chen 2003 ³⁶	(196)	71 (36%)		55 (77%) [38 (53%) detected by mammogram only] 17 (24%) detected by both mammogram + clinical exam	33 (46%) [16 (23%) detected by clinical exam only]	
Yau 2007 ³⁷	511 (36)	13 (2.5%)	1 (8%)	8 (62%)	3 (23%)	1 (8%)
Robinson 2007 ³⁹ – younger (<40) cohort	(90)			17%		
Robinson 2007 ³⁹ – older (55-59) cohort	(108)			56%		
Montgomery 2007c ³¹	1312 (108)	35 (2.6%)	8 (23%)	25 (71%)	2 (6%)	

*study as regional nodes

[^] local recurrence in conserved breast

[†] includes ipsilateral breast and/or axilla. contralateral and bilateral breast recurrence

[€] ipsilateral breast and/or axilla

~defined as metachronous tumours

‡detected by clinician

Table 7 Accuracy of tumour markers

Study	Serum Markers	Sensitivity	Specificity
Anan 2002 ⁴²	CEA	33.3%	99.2%
	CA15-3	28.6%	98.3%
	TPA	64.3%	94.2%
	NCC-ST-439	36.4%	92.5%
	BCA225	11.1%	97.5%
Kokko 2002 ⁴³	CA15-3	13%	99%
Nakamura 2005 ⁴⁴	CEA	54.3%	93.6%
	CA15-3	57.1%	99.5%
Nicolini 2006 ⁴⁵	<i>MCA >11U/mL *</i>		
	MCA	68%	42%
	CEA	10%	-
	TPA	26%	-
	CA15-3	32%	-
	MCA-CA 15-3	68%	40%
	CEA-TPA-CA 15-3	53%	59%
	<i>MCA >15U/mL *</i>		
	MCA	53%	73%
	CEA	16%	96%
	TPA	42%	42%
	CA15-3	32%	97%
	MCA-CA 15-3	58%	71%
CEA-TPA-CA 15-3	74%	69%	
Valenzuela 2003 ⁴⁶	CA15-3	47.4%	88.4%
	CA15-3/CEA	56.8%	85.3%

*cut off values

- ***Does intensive follow-up provide benefits over standard follow-up?***

A Cochrane review, published in 2000 and updated in 2004, reported a meta-analysis of two RCTs comparing standard and intensive follow-up that were published prior to 2000.¹⁹ The Cochrane review found no difference in overall mortality between non-intensive and intensive follow-up strategies (OR:0.96; 95% CI: 0.80, 1.15; p=0.7). Similar results were found for disease-free survival (OR: 0.84; 95% CI:0.71, 1.00; p=0.05).¹⁹

Description of studies

Three trials have been published since 2004 that investigated differences between standard (clinical) and intensive follow-up, two RCTs^{47, 48} and one prospective non-randomised cohort.⁴⁹ Details of these trials and the definitions of follow-up are in Table 8.

Table 8 Study characteristics of papers comparing standard vs intensive follow-up

Study	Design	Population	Standard follow-up	Intensive follow-up
Bornhak 2007 ⁴⁹	Prospective non-randomised cohort Multi-centre, Germany Enrolled Dec 1995 – Feb 2000 Patients followed for 5yrs	N=670 <50yr: 33% vs. 37% 50-70yrs: 67% vs. 63% T1: 59% vs. 46% T2: 33% vs. 42% T3 or T4: 8% vs. 12%	Structured physician checklist (including history and physical examination), checklists sent every 3mths for 1 st 3yrs, every 6mths 4 th and 5 th yrs and yearly thereafter. Mammography of contralateral breast yearly and ipsilateral 6mthly for first 3yrs then yearly after NB Special interest paid to patient complaints: newly developed pain, nausea, loss of appetite, cough, shortness of breath, vision disturbances, discomfort or fatigue	Same as in standard follow-up plus chest x-ray and liver ultrasound every 6mths and laboratory tests every 3mths during first 3yrs then every 6mths after
Kokko 2005 ⁴⁷	RCT Single centre? Area of 1 hospital in Finland Median follow-up 4.2yrs	N=472 Women with localised BC diagnosed May 1991 – Dec 1995 Median age 59.7 vs. 56.9 T1: 65% vs. 64% T2: 32% vs. 33% BCT: 46%* Mastectomy: 52%*	3mthly or 6mthly visits and when clinically indicated: blood tests HB, WBC, platelet count, calcium, sedimentation rate, liver enzymes, and CA15-3, chest x-ray, liver ultrasound and bone scan	3mthly or 6mthly visits including routine blood tests HB, WBC, platelet count, calcium, sedimentation rate, liver enzymes, and CA15-3 every visit, chest x-ray every 6mths, liver ultrasound and bone scan every 2 nd year
Oltra 2007 ⁴⁸	RCT Single centre: 1 hospital in Spain Recruited Jan 1997 – Dec 1999 Median follow-up 3yrs	N=121 Women attending oncology clinic after diagnosed with stage I, II or III BC who had completed an initial curative treatment. Median age: 53 vs. 54yrs; range: 35–69yrs	Careful history and physical examination, no complimentary tests undertaken if the clinical symptoms at the time didn't require them All patients had annual mammography Outpatient appointments scheduled every 4mths in 1 st year, every 6mths 2 nd – 6 th year, annually thereafter	In addition to anamnesis and physical examination, biochemistry, hematogram and markers CEA and CA15-3 were assessed at every outpatient visit together with an annual hepatic echography, chest x-ray and bone scan All patients had annual mammography Outpatient appointments scheduled every 4mths in 1 st year, every 6mths 2 nd – 6 th yr, annually thereafter

Note: BC=Breast Cancer; BCT=breast conserving therapy; mths=months; RCT=randomised controlled trial; yr=year

Outcomes

Rates of recurrence and death for the trials are reported in Table 9. The three studies found no difference in detection of recurrence between the clinical or intensive follow-up arms. A previous publication by Kokko *et al* reported no difference in 5 year DFS or OS.⁵⁰ The other study which reported on overall survival also found no difference in 5 year OS or RFS between study arms.⁴⁹

Two of the trials^{47, 48} reported on economic outcomes of intensive follow-up, these results are discussed later in this report.

Table 9 Standard vs. intensive follow-up results

Study	Group	Recurrence	Disease free survival	Death	Overall survival
Bornhak 2007 ⁴⁹	Standard n=426	73 (17%)	5yr RFS: 82%	32 (7.5%)	5yr OS: 92%
	Intensive n=244	41 (17%)	5yr RFS: 82%	28 (11.5%)	5yr OS: 88%
			Intensive vs. clinical HR: 1.23 (95% CI: 0.53, 1.52)		Intensive vs. clinical HR: 0.90 (95% CI: 0.53, 1.52)
Kokko 2005 ⁴⁷	Standard n=229	63 (28%)			
	Intensive n=243	59 (24%)			
Kokko 2003 ⁵⁰	Standard n=229		5yr DFS: 89%		5yr OS: 85%
	Intensive n=243		5yr DFS: 86%		5yr OS: 88%
Oltra 2007 ⁴⁸	Standard n=63	11 (17%)			
	Intensive n=58	13 (22%)			

CI – confidence interval; DFS – disease-free survival; HR – hazard ratio; mth=month; OS – overall survival; RFS – recurrence-free survival; yr=year

- **What is the optimal interval and duration of follow-up care?**

Description of studies

One RCT reported on the difference between having follow-up tests (either standard or intensive) every 3 months or every 6 months.⁴⁷ This trial had four arms: i) intensive follow-up every 3 months, ii) standard follow-up every 3 months, iii) intensive follow-up every 6 months and iv) standard follow-up every 6 months. The main outcomes of this trial were OS, DFS and cost.

A retrospective analysis of breast cancer patients with CBC reported on the difference between yearly or biennial mammography.⁴¹ Another trial reported on women who had a mammogram within 1 or 2 years prior to death/censoring compared to women who did not have a mammogram within 2 years.⁵¹ The remaining two case-control trials reported on the influence of having regular surveillance mammograms after breast cancer treatment on survival in older women (≥ 65 years).^{52, 53}

Outcomes

Frequency of follow-up visits

Kokko *et al* reported that DFS and OS did not differ between the four groups, standard or intensive visits every 3 or 6 months.⁴⁷ However, by having visits every 3 months instead of every 6 months, the cost was increased 1.4 times.⁴⁷

Table 10 Detailed overall and disease-free survival information from Kokko *et al*

Regimen	Overall survival	Disease-free survival
3 monthly, intensive tests	82%	74%
3 monthly, standard tests	74%	67%
6 monthly, intensive tests	85%	73%
6 monthly, standard tests	84%	72%
All groups	81%	72%

* Information provided by R. Kokko, personal communication

Frequency of tests

Kaas *et al*⁴¹ report on the impact of mammographic interval (annual or biennial) on survival after diagnosis of CBC. Five-year DFS was 75% in both the annual and biennial mammography groups.

A study of women aged 65 or older found that compared to women who did not have any mammograms within a two year period (prior to death/censorship), women who had a mammogram within a one or two-year time interval had a lower risk of breast cancer-specific mortality (within one year OR: 0.83, 95% CI: 0.72, 0.95; within two years OR: 0.80, 95% CI: 0.70, 0.92) and all-cause mortality (within one year OR: 0.83, 95% CI: 0.76, 0.90; within two years OR: 0.72, 95% CI: 0.66, 0.78).⁵¹

While not indicative of how many regular surveillance mammograms breast cancer patients should have and at what frequency, studies have shown that having more than one routine surveillance mammogram after breast cancer treatment is associated with lower mortality.^{52, 53} A study of 178 women aged 65 or older who died of breast cancer found that each additional routine surveillance mammogram was associated with decreased breast cancer mortality (OR: 0.69; 95% CI: 0.52, 0.92).⁵²

Duration of follow-up care

No primary studies were identified which addressed how long follow-up care should continue after diagnosis/treatment.

3.3.2 Provision of follow-up care

- ***Does the person who provides follow-up care influence outcomes?***

Description of studies

Three RCTs,⁵⁴⁻⁵⁶ and one non RCT⁵⁷ were identified which investigated the provider of follow-up care. The four studies included in this section varied in the comparison of follow-up providers used,⁵⁴⁻⁵⁷ see Table 11. Different providers investigated were specialists, GPs and nurses.

Table 11 Study characteristics of provider of follow-up trials

Study	Design	Population	Follow-up models
Brown 2002 ⁵⁴	RCT	N=61	i) Standard clinic follow-up Attended clinic as usual, examined by a doctor and had the opportunity to ask questions. Yearly mammograms were performed.
	Multi-centre: 4 clinics from 1 hospital, 1 clinic from another hospital, UK	Mean age: 63yr vs. 68yr, range: 48–87 T1: 19% vs. 30%; T2: 81% vs. 70%	ii) Patient-initiated: patients received written information on the signs and symptoms of recurrence. Patients did not attend routine appointments but were advised to contact breast care nurse if they experienced a problem. Yearly mammograms were performed
	Patients assessed for 1yr	Wide excision: 29% vs. 37%; wide excision + axillary clearance: 45% vs. 20%; mastectomy: 0 vs. 10%; mastectomy + axillary clearance: 26% vs. 33%	
Grunfeld 2006 ⁵⁵	RCT	N=968	i) Follow-up in cancer centre Not defined
	Multi-centre: 6 regional cancer centres in Ontario, Canada	EBC Mean age: 61yrs (range 25–92)	ii) Follow-up by family physician: physician provided with one page guideline on follow-up that recommended physical exam and medical history every 3-6mths for 3yrs, every 6mths for 2yrs and then yearly indefinitely; mammograms yearly indefinitely; diagnostic tests to investigate signs/symptoms if clinically indicated; For women on tamoxifen, the guideline recommended a history of vaginal bleeding be taken at each visit & pelvic examination yearly. Instructed to refer patient back to cancer centre if new recurrence or primary breast cancer developed
	Enrolled: Jan 1997 – Jun 2001	Lumpectomy: 74%*; mastectomy 20%*; biopsy only: 7%*	
	Median follow-up 3.5yrs		
Koinberg 2004 ⁵⁶	RCT	N=264	i) Physician: 4 visits per year for first 2yrs then biannual for up to 5yrs then annual. History and clinical examination each visit, mammogram annually, blood tests/ chest x-ray/imaging techniques on clinical indication History – included symptoms that could signal a loco-regional relapse or distant metastases Clinical exam – breasts, chest wall and regional lymph nodes
	Multi-centre: 3 hospitals in Sweden	Mean age: 59* (<40:3%*; 40–49:19%*; 50–59:27%*; 60–69: 38%*; 70–79:15%*) T1: 45%*; T2: 55%*	ii) Nurse-led: mammogram yearly, after 3yrs patient referred back to routine mammography screening program. Nurse gave advice on aspects of self care. Patients contacted nurse if they had questions or symptoms that could be related to breast cancer
	Enrolled: Jan 1991 – Nov 1996		
Koinberg 2006 ⁵⁷	Non-random longitudinal	N=96	i) Physician: twice a year for 2yrs followed by annual exams for 5yrs and annual mammogram. Blood tests, chest x-ray, or other imaging performed on clinical indication. Examination included history taking concerning symptoms that could signal loco-regional or distant relapse as well as clinical examination of breasts, chest wall and regional lymph nodes.
	2 hospitals in Sweden (one for the intervention, the other control)	Stage I/II BC Mean age: 62yr vs. 60yr Stage I: 27 (59%) vs. 36 (72%) Stage II: 19 (41%) vs. 14 (28%)	ii) Multidisciplinary educational programme: led by a nurse in collaboration with physiotherapist, social worker, physician and advocacy group member. Women could contact nurse if required. All were referred to routine Swedish mammography-screening program (mammogram every 18–24mths for women 40–74yrs)
	Enrolled Jan 2001 – Sept 2002		
	Patients assessed for 1yr	Mastectomy: 22 (48%) vs. 6 (12%) Partial mastectomy: 24 (52%) vs. 44 (88%) P<0.001	

Note: * average between two arms; mth=month; yr=year

Outcomes

Only two trials reported on OS and recurrence outcomes, however all trials reported on quality of life outcomes.

Overall survival

Grunfeld *et al*⁵⁵ reported that there was no difference in the number of deaths in the family physician group (29 deaths, 6%) and the cancer centre group (30 deaths, 6.2%), see Table 12. Similarly, Koinberg *et al* (2004)⁵⁶ reported 14 deaths (11%) in both the physician and the nurse-led group.

Detection of recurrence

Grunfeld *et al*⁵⁵ reported that there was no difference in the number of recurrences detected in the family physician group (11.2%) and the cancer centre group (13.2%). This study also reported on recurrence-related serious clinical events (SCEs) defined as any one of spinal cord compression, pathologic fracture, hypercalcemia, uncontrolled local recurrence, brachial plexopathy or poor functional status. The rate of SCEs was low and there was no difference between the rate in the family physician group (3.5%) and the cancer centre group (3.7%).⁵⁵

Koinberg⁵⁶ did not report any statistical difference between the number of recurrences detected in the physician group compared to the nurse-led group.

Table 12 Provider of follow-up and recurrence and survival

Study	Provider	Patient numbers	Recurrence	Overall survival
Grunfeld 2006 ⁵⁵	Cancer centre	485	64 (11.2%)	30 deaths (6.2%)
	Family physician	483	54 (13.2%)	29 deaths (6.0%)
Koinberg 2004 ⁵⁶	Physician	131	8 locoregional, 9 distant	14 (11%)
	Nurse-led	133	12 locoregional, 9 distant	14 (11%)

Quality of Life

Quality of life was assessed in these trials using various validated scales and questionnaires, including the Functional Assessment of Cancer Therapy-Breast/General (FACT-B/G), EORTC QLQ-C30, EORTC QLQ-BR23, Short-Form 36 (SF-36) Mental Component Summary/Physical Component Summary (MCS/PCS), Self-Care Aspects (SCA) and Sense of Coherence (SOC) questionnaires and the Hospital Anxiety and Depression (HAD) and Satisfaction and Accessibility (SaaC) scales.

Standard clinic follow-up vs. patient initiated follow-up

A RCT by Brown *et al*⁵⁴ compared standard clinic follow-up to patient initiated follow-up among 61 breast cancer patients in remission. Those in the clinic follow-up scored higher in the arm and breast symptoms scale in the EORTC questionnaire for QoL (at baseline, 6 months and 12 months). In terms of psychological morbidity there was no significant difference between the groups on the HAD scale. With regard to satisfaction with follow-up, more women in the patient initiated group reported convenience as an advantage, while more women in the clinic follow-up reported reassurance as an advantage.

Cancer centre follow-up vs. family physician

Grunfeld *et al*⁵⁵ reported a RCT of 968 early breast cancer patients, comparing follow-up in a cancer centre to follow-up by a family physician. Using three scales; HADS, SF-36 MCS and SF-36 PCS, there was no significant difference among the two groups in relation to health related quality of life.

Nurse led follow-up vs. physician follow-up

Koinberg *et al*⁵⁶ conducted a RCT among 264 breast cancer patients. The trial used two scales to compare QoL; HAD and SaaC, there was no statistically significant difference between the two groups in either of the scales. Generally the levels of anxiety and depression were low.

In 2006 Koinberg *et al*⁵⁷ reported on a non-randomized longitudinal study which compared a multidisciplinary educational program led by a specialist nurse and physician follow-up. Three scales were used to measure QoL among the 96 participants; FACT-G, SCA and SOC scales. In the FACT-G scale women in the multidisciplinary educational program rated worse than physician-led patients with regards to physical wellbeing. There were no statistically significant differences between the two groups with regard to coping ability, participation in decision-making and knowledge about the disease in the SCA scale. In the SOC scale, there were no statistically significant differences between the two methods at baseline or at 1 year. Women in the physician follow-up group scored lower (worse) SOC one year after diagnosis.

Transfer of care to primary care

Investigations of the transfer to primary care were predominately qualitative however a single quantitative study by Grunfeld *et al*,⁵⁵ found that 55% of the patients approached for the study agreed to participate showing that while the majority of patients were willing to be followed by a family physician, some patients may find this unacceptable.

When asked about transfer of care to a primary care provider from an oncologist, a survey by Nissen⁵⁸ found that many primary care providers expressed uncertainty about what tests should be ordered and how frequently or how long these should be ordered.

Vanhuyse *et al*⁵⁹ evaluated the feasibility of transferring patients from oncologist to the family physician for follow-up care. Of 193 people, 83 patients were considered suitable for transfer back to the family physician. Reasons for unsuitability included clinical trial enrolment, ongoing endocrine treatment, new symptoms and, in one case, patient refusal. Nearly 58% of those who were transferred back to their family physician were also being followed by other oncologists (surgical and/or radiation) indicating a duplication of effort. To facilitate transfer of patients in this study, both the patient and the family physician were given information packages outlining current guidelines for follow-up and adverse effects and signs and symptoms to be aware of. A rapid re-referral form and process were available to the family physician to facilitate referral to the medical oncologist if a recurrence is suspected.

McCaughan⁶⁰ found in an interview of 13 medical & nursing staff that they considered that appropriately prepared nurses could review patients.

- ***Do shared care models of follow-up influence outcomes?***

Description of studies

Only one study explicitly examined the use of shared care⁶¹ however other trials reported on provider of follow-up care, and in many cases patients were seen by a variety of specialists. The shared care study included a cohort of 3828 women, data was collected on which specialities of physicians were seeing the patient, see Table 13. Generalists were defined as physicians identified as general practice, family practice and general internal medicine. Breast cancer specialists were defined as general surgeons (including surgical oncologists), radiation oncologists and medical oncologists/haematology oncologists.

Table 13 Shared care models of follow-up

Study	Design	n	Demographics	Follow-up models
Etim 2006 ⁶¹	Cohort	3828	Mean age: 74.5yrs T1: 56.3% T2: 30.1%	i) Generalists only ii) Breast cancer specialists only iii) Both generalists and breast cancer specialists (shared care) iv) Other specialists exclusively

Outcomes

This study of older breast cancer survivors (mean age 75 years) found that approximately 66% underwent shared care (generalist physicians and specialists). Women with shared care had a higher rate of mammography use than those who did not use shared care (in the 1st follow-up year OR: 1.14, 95% CI: 1.11, 1.17; in the 2nd follow-up year OR: 2.23, 95% CI: 1.88, 2.65). Women who saw breast specialists only or who had shared care had a higher likelihood of undergoing mammography than women who saw generalists only (OR: 1.44, 95% CI: 1.13, 1.83 and OR: 2.29, 95% CI: 1.81, 2.90 respectively).⁶¹

- ***What are the patient's preferences for follow-up models of care?***
- ***What evidence surrounds the role of follow-up care in psychosocial outcomes of women?***

Although these two questions were separate when developing the search strategy for this review, when the papers were reviewed it was found that the majority of papers described the experience of follow-up care rather than specifically patient preferences or psychosocial outcomes. Therefore these two questions will be considered together. The first question was originally on patient preferences however information was identified on patient perceptions and needs from follow-up care as well as physician preferences for follow-up care, so this additional information has been included.

Description of studies

Studies relating to patient and/or physician perceptions and preferences of follow-up care used qualitative research methods such as surveys/questionnaires, focus groups or interviews to identify themes and opinions. Some studies were small with only 6 to 30 participants however some questionnaires collated information from hundreds of patients and/or physicians. The details of follow-up care were often not provided in these studies.

Outcomes

Patient perceptions/needs of follow-up care

A key theme for patients undergoing follow-up was the fear of recurrence and the need for reassurance that they were still disease-free.^{60, 62-66} For some patients attending follow-up visits was a cause for anxiety,^{60, 63, 65, 67-69} however this was often reduced after attending the follow-up visit.⁶⁸

Another theme that came up in multiple papers was the need for continuity of care.^{62, 68, 70} The study by Renton *et al* found that 58% of patients preferred to see the same person at follow-up appointments.⁶⁸ Continuity of care allows a patient-doctor relationship to form which Kelly *et al*⁶² found improved comfort of patients as the doctor was familiar with their case.

Some papers suggested that women's psychosocial needs were not being met, often due to time constraints with clinics being very busy.^{60, 65, 69} In a cross-sectional survey of 24 women, 19 (79%) reported they did not feel comfortable raising any emotional/psychosocial concerns at their routine visits.⁶⁹

Frequency of follow-up visits

Patient preferences

de Bock *et al*⁷¹ reported on a survey of 84 women and found that the majority of patients (59%) would prefer to attend routine clinical visits every six months, 25% would prefer to attend every 3 months and 16% every year. After observation of consultations, Beaver *et al*⁶³ report that changing follow-up visits from 3 monthly to 6 monthly did not cause concern for patients, however changing from 6 months to 12 months, or even discharge, created anxieties for some women who appeared to depend on follow-up as a means of detecting recurrence.

The survey by de Bock *et al*⁷¹ also found that most patients (66%) would like to attend life-long follow-up, compared to 22% who would like to attend follow-up visits for 10 years and 12% who would like to attend visits for 5 years after diagnosis. A questionnaire of 73 patients with a history of BC found that approximately 33% thought that supervision by a breast specialist for up to 5 years after diagnosis was sufficient, and 46% indicated that the breast specialist should follow-up the patient for 10 years or longer.⁷²

Physician preferences

A questionnaire of 562 specialists⁷³ found the preferred median follow-up duration was for 5 years. Factors predicting delayed discharge were younger patients, treatment factors such as ongoing hormonal therapy or treatment related morbidity and patient risk factors such as breast cancer family

history. A smaller questionnaire, including 22 physicians, found that approximately 33% physicians thought supervision by a breast specialist for 5 years was sufficient and 59% thought follow-up should continue for 10 years or longer after initial diagnosis.⁷²

Provider of follow-up care

Patient preferences

de Bock *et al*⁷¹ reported that 86% of patients preferred to be followed up by a hospital doctor, 7% by a GP, 6% by a specialised nurse. Renton *et al*⁶⁸ report that 39% preferred to talk to the consultant regarding breast cancer and 77% expressed confidence in the consultant regarding breast cancer care; 44% expressed a desire to talk to a specialised nurse however only 33% expressed confidence in the specialist nurse regarding breast cancer care; 16% expressed confidence in their GP in this setting. However Renton *et al* also found that 39% of women indicated they would be happy with their GP being responsible for follow-up, 67% indicated they would be happy with a specialist nurse talking responsibility for follow-up.⁶⁸ Miedema *et al*⁷⁴ reported that 36% of the BC patients in their study reported dissatisfaction with family physician compared to 19% dissatisfaction with specialist. An older survey by Pennery⁶⁹ found that of 24 breast cancer patients, 38% considered that follow-up care should be provided only by a doctor, 54% suggested that it should be provided by a breast cancer nurse and 8% thought a combination would be best.

Koinberg *et al* interviewed 19 women who were involved in nurse-led follow-up voluntarily. Patients satisfaction with the knowledge and professional skills of the nurses was high.⁷⁵

Physician preferences

A questionnaire by Nissen *et al*⁶⁸ found that 49% of primary care providers were comfortable with having responsibility for surveillance for BC recurrence and 41% were confident following standard guidelines for surveillance of breast cancer recurrence. Another questionnaire of 562 specialists found that 60% indicated that the breast surgeon takes primary charge of follow-up, when asked about the contribution of primary care in follow-up, 70% thought the main advantage for this would be reduced clinical workload however main disadvantages noted were lack of GP experience or training in oncology and loss of patient outcome data.⁷³

Intensive surveillance

Patient preferences

A survey of 84 breast cancer patients found that 82% preferred additional investigations to be part of routine follow-up,⁷¹ another survey found that expectations of intense follow-up included an increased sense of security and reassurance and decreased fear and distress.⁷⁶

Psychosocial support

In the survey by de Bock *et al*⁷¹ a small percentage of patients indicated they would be interested in receiving information about the following topics as part of their follow-up:

- information on breast cancer self-help groups (19%)

- consultation with psychologist or psychiatrist (8%)
- consultation with hospital social worker (17%)
- consultation with pastoral care provider (6%).

However, the remaining patients either indicated that these topics were not important and they did not want this information or they were indifferent as to whether this information should be included or not.

In another study 83% of breast cancer patients expressed a desire for counselling from either their family physicians or specialists.⁷⁴

- ***Are there subsets of the defined population who have specific follow-up requirements?***

Description of studies

No studies were identified which directly examined different follow-up requirements for any subsets of patients with breast cancer.

One trial reported that older patients were more likely than younger patients to have CBC detected by mammography (56% vs. 17%; $p < 0.001$), younger patients more likely to have CBC detected by physical examination or self-examination.³⁹

Some studies were identified which examined patterns of follow-up care, and which noted differences in receipt of follow-up care/tests. However these studies were excluded from the review as they were not considered relevant because they were based in the United States (US) so not generalisable to the Australian setting. These trials did report some differences in receipt of follow-up care between groups such as older/younger patients, minority groups and rural/urban populations.

- ***Economics of follow-up***

Kokko *et al*⁷⁷ reported that the most expensive tests were bone scans and blood tests. This trial showed that by having tests every 6 months instead of 3 months **and** ordering additional tests based on clinical indication (standard follow-up) rather than routinely (intensive follow-up), costs of follow-up can be halved with no adverse impact on OS or DFS.

Oltra *et al*⁴⁸ report that the overall cost of intensive follow-up was 3 times more expensive than standard clinical follow-up with no difference in detection of recurrence.

Hensley *et al*⁷⁷ observed the economic consequences of surviving breast cancer. They surveyed 245 patients from the CALGB 8541 trial and found that the costs associated with follow-up are higher with medical oncology follow-up and among younger and lower income survivors, likely due to frequent use of tumour markers and bone scans. This study also found that few women reported adverse long-term economic effects of breast cancer on employment and/or insurance status (84–85% reported the overall impact as neutral).⁷⁷

A French study analysed the economic impact of compliance to follow-up guidelines for breast cancer (three clinical consultations per year for two years, followed by two consultations per year for next three years, one mammogram per year for five years; further investigations only performed in case of symptoms). Noncompliant follow-up utilised more tumour marker tests, chest x-rays, liver ultrasounds and bone scans than follow-up which was compliant to the guidelines. Expenditures were less than half the cost for clinical practice guideline (CPG) compliant follow-up compared to noncompliant follow-up.⁷⁸

Treatment-related toxicities

While many of the primary studies acknowledge that follow-up can identify treatment-related toxicities, there were no specific requirements identified for follow-up procedures other than discussing symptoms/problems with the patient.

Many side effects are due to chemotherapy or endocrine therapy. Some of the effects will cease once treatment is finished however a list of long-term side effects of treatments for breast cancer can be found at Appendix 6.

The ASCO guidelines⁷ recommend gynaecologic follow-up (pelvic examination), especially for patients on tamoxifen due to the increased risk for developing endometrial cancer associated with this drug. Both the ASCO⁷ and Health Canada¹¹ guidelines recommend that the clinician asks about vaginal bleeding.

Previous NBCC[§] guidelines note that newer drug therapies, such as aromatase inhibitors and trastuzumab, have individual side effect profiles. In particular, aromatase inhibitors can be associated with reduction of bone mineral density and trastuzumab can be associated with cardiac dysfunction. NBCC recommend that patients receiving these drugs should be reviewed regularly and monitored for side effects by clinicians familiar with the drugs.^{79, 80}

A common treatment-related toxicity is secondary lymphoedema, affecting approximately 20% of breast cancer survivors.⁸¹ Secondary lymphoedema can appear at any time after surgery or radiotherapy however approximately 70-80% of lymphoedema after breast cancer presents within the first 12 months.⁸¹ NBOCC secondary lymphoedema guide for health professionals states that assessment of patients may be undertaken by checking personal history and conducting a physical examination of the affected limb/body part to detect swelling. It is important to be aware of signs and symptoms of lymphoedema as early diagnosis and treatment of the condition appears to be an important factor in the success of treatment.⁸¹ If swelling is detected the health professional may initiate management options and regularly review the patient or refer to an appropriately trained lymphoedema practitioner or clinic if symptoms are severe or unresponsive to initial management.⁸²

[§] In February 2008, National Breast Cancer Centre, incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

3.4 Ongoing trials

The following clinical trials websites were searched to identify any additional follow-up studies which have not yet reported.

- Australian New Zealand Clinical Trials Registry (ANZCTR) <http://www.anzctr.org.au/>
- Clinical Trials.gov <http://www.clinicaltrials.gov/>
- Current Controlled Trials <http://www.controlled-trials.com/>
- National Research Register <http://www.nrr.nhs.uk/>
- National Cancer Institute <http://www.cancer.gov/clinicaltrials>
- World Health Organisation (WHO) International Clinical Trials Registry Platform <http://www.who.int/trialsearch/> .

Two RCTs were identified as ongoing trials.⁸³⁻⁸⁵ Details of the trials are presented in Table 14.

Table 14 Ongoing studies investigating follow-up after breast cancer treatment

Title/trial name	Location/s	Status	Participants	Intervention	Objectives
Improving the efficiency and quality of follow-up after curative treatment for breast cancer					
MaCare trial/ ISRCTN74071417 ⁸³ ⁸⁴	Netherlands	Completed accrual	Breast cancer patients without distant metastases within 6wks after treatment N=320	i) standard follow-up ii) nurse-led follow-up iii) similar to arm i plus educational group program iv) similar to arm ii plus educational group program	Primary outcome: Cancer specific QoL. Secondary outcomes: perceived feelings of control, anxiety, patients satisfaction and costs.
A randomised trial of a patient-centred strategy to facilitate transition of breast cancer survivors' routine follow-up from specialist to primary care					
Follow Up II (OCOG) ⁸⁵	Canada	Recruiting	Women with invasive breast cancer having completed primary treatment	i) usual care (specialist) ii) family practitioner follow-up	Primary outcome: specific health related QoL Secondary outcome: other HRQoL domains

Note: HRQoL: Health related quality of life; Wks=weeks

4 Discussion

Many international guidelines for follow-up of breast cancer patients were identified, however most were general in nature. Common elements include recommending regular physical exam and mammography, however there is no clear guideline on frequency or duration of follow-up care. All of these current guidelines acknowledge a paucity of definitive evidence.

Eight systematic reviews were identified, although limited definitive information on follow-up procedures was obtained through these. No review found trials to recommend frequency or duration of follow-up.

Limited high quality quantitative information was available on follow-up care after breast cancer. Five RCTs were identified, three on provider of follow-up care, and two on standard (history, physical exam & mammography) compared to intensive (standard plus routine diagnostic tests such as blood tests) follow-up. The RCTs were reported after a maximum of 5 years post-diagnosis therefore there is no long-term data on the effects of the different follow-up schedules. Much information on follow-up was from comparative and observational studies, and some additional information was identified through qualitative research such as surveys, focus groups and interviews.

There were some limitations in the papers identified, particularly varying definitions between trials. The follow-up care provided differed greatly between trials not only between standard or intensive tests being used but also in the frequency of follow-up visits and the components of physical examination performed (often not reported in detail). Trials also reported recurrences differently where some papers defined recurrence as including local and distant recurrences as well as contralateral breast cancers, others reported CBC as a separate event. The populations included in the trials were reasonably similar, with trials including early breast cancer, most included women of all ages and excluded patients participating in other clinical trials. With regards to the treatment given prior to follow-up, some trials focused on patients having BCT only, others included patients having any kind of surgery (e.g. mastectomy \pm axillary clearance; BCT \pm axillary clearance).

Follow-up tests

Method of detection

Women with asymptomatic recurrence were more likely to be diagnosed at an earlier stage of disease than those who were symptomatic at time of diagnosis.²⁶⁻²⁹ Most asymptomatic recurrence was detected by clinical examination.²⁶⁻²⁸ One study reported recurrence diagnosed while asymptomatic has a significantly longer median survival.²⁶ te Boekhorst *et al* found that while initially survival appeared to be better for asymptomatic patients, when the analysis was done separately for locoregional and distant recurrence there was no longer a significant difference in survival.²⁷ Differences in survival may be due to tumour characteristics/favourable prognostic factors e.g. slow-growing tumours more likely to be detected while asymptomatic (length-time bias), fast-growing tumours (more aggressive) more likely to present symptomatically.²⁶ The studies did show that local recurrences are more likely to be detected while asymptomatic.²⁶⁻²⁹ Another bias may be lead-time bias where patients with disease detected prior to development of symptoms appear to live longer even if there is no treatment effect.²²

Symptomatic disease tends to present in between routine follow-up visits, however reported rates of interval visits identifying recurrence range from 21%³² to 76%.²⁹ The meta-analysis by de Bock *et al* found that 41% of locoregional recurrences were diagnosed outside routine visits however 18% presented with symptoms during a routine visit.²²

Detection of contralateral breast cancer by mammography appears to relate to better outcomes in terms of prognostic characteristics³⁴ and overall survival than detection by physical examination.^{39, 41} However, while Montgomery *et al* reported that for patients with ipsilateral breast cancer recurrence, detection by mammography was associated with improved survival, method of detection did not impact survival for patients with axillary relapse or new CBCs.³¹ Doyle *et al* reported that detection of local recurrence by mammography or a combination of mammography and clinical exam had improved survival compared to detection by clinical exam alone, however on multivariate analysis method of detection was not an independent predictor of survival.⁴⁰ Differences in survival may be due to tumour characteristics/favourable prognostic factors e.g. smaller or slow-growing tumours more likely to be detected by mammography however Montgomery *et al* reported that there was no significant difference in any clinicopathological features in relation to how relapse was detected.³¹

A Cochrane review published in 2000, and updated in 2004, included two RCTs which compared intensive to clinical follow-up. Articles published since this Cochrane review support the conclusion that intensive follow-up does not provide an additional overall or disease-free survival benefit compared to standard follow-up.¹⁹

While intensive follow-up has been found to have limited benefit for patient outcomes, the use of tumour markers has become more advanced since the previous NBCC^{**} guidelines were published. Overall, tumour markers have a low sensitivity but a high specificity for detection of recurrence of breast cancer. It is interesting that the lead time of tumour markers to definitive diagnosis can be significant – ranging from 60 days⁴⁵ to 334 days.⁴⁴ Further information is needed to determine the use of tumour markers in routine follow-up.

Interval/duration

The optimal interval and duration of follow-up remains an area with minimal research evidence. One RCT found that increasing frequency or interval of tests (3 monthly vs 6 monthly) does not affect DFS or OS, however does increase costs.⁴⁷ Studies have shown that attending more than one routine surveillance mammogram after breast cancer treatment lowers breast cancer mortality.^{52, 53} However reduction of mammograms to none in a two year period appears to negatively affect mortality.⁵¹ A potential confounding factor in these studies is that women who attend regular visits may be more likely to seek medical attention for signs or symptoms of recurrence which may lead to earlier detection and better prognosis. Women who attend regular visits may also be associated with factors such as health behaviours and physical function which may also confound the relationship.⁵² Further clinical trial information is needed to determine the optimal interval and duration of follow-up visits and tests.

^{**} In February 2008 National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

Provision of Follow-up Care

Follow-up care provider

The person providing follow up care does not appear to influence outcomes such as overall survival or detection of recurrence.^{55, 56} Similarly, patient QoL appears to be minimally affected by different providers of follow-up care.⁵⁴⁻⁵⁷ Long-term data is currently not available as these trials had a maximum follow-up of five years.

Shared care

There has been little research into shared care, and while it appears that shared care influences the way follow-up is provided, it is not clear if this influences outcomes.⁶¹

Patient preferences/perceptions

Patient needs and preferences for follow-up treatment vary and are influenced by many factors. A key theme identified was the provision of reassurance that they were disease free through follow-up visits, despite the increased anxiety associated with anticipation of the visit.^{60, 62-65, 67-69} This may influence patients' preferences for more frequent visits (6 monthly) and ongoing (life-long) follow-up,^{63, 71} or at least long-term follow-up (10 years).⁷²

While provision of care by a nurse or GP appears acceptable to women, a specialist or hospital doctor appears to be preferred.^{68, 71} One survey found that less than half of primary care physicians feel comfortable providing follow-up care.⁵⁸

Subgroups

No trials were identified which addressed specific requirements for particular subgroups of women (such as women at high risk of recurrence, younger women etc), The limited evidence means that requirements of specific groups are not able to be determined. However, factors which may need to be considered when planning follow-up care include use of long-term hormonal therapy, age and hormonal status, genetic factors, socio-economic status, accessibility of services and availability of clinical trials.

5 Conclusions

This NBOCC review included 73 papers published between January 2000 and January 2008, including five RCTs.

One aim of follow-up is to detect recurrences or new CBCs. Self-detection, routine mammography and routine clinical examination all play a part in detection of recurrences and CBCs. The reported rates that each method contributed to detection vary between papers, however many papers report that over 50% of recurrences or new breast cancers are detected by the patient. Women should be aware of potential signs and symptoms of recurrence.

Intensive follow-up provides no additional survival benefit compared to standard follow-up.

The follow-up care provider does not appear to influence survival or psychosocial outcomes, however trials are limited to maximum of five years duration.

This review does not provide information on the optimal duration or interval for follow-up care.

The psychosocial needs of women following breast cancer treatment vary. Reassurance that the cancer had not returned was the most commonly reported psychosocial outcome for patients.

There is limited information on how follow-up care is being performed in Australia. Longer follow-up and further research is needed to determine the optimal schedule, duration and provider of follow-up care.

Appendix 1 NHMRC Levels of Evidence²

Table 1.3 Designation of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly-designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pretest/post-test.

Source: NHMRC 1999

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Appendix 2 Literature databases searched

Source	Results/Retrievals
Medline (Ovid)	2246
Embase	2852
Pubmed	2015
CINAHL	533
PsycINFO	156
Additional Papers (sourced from reference lists)	6

Appendix 3 Health technology assessment, guidelines and clinical trials websites searched

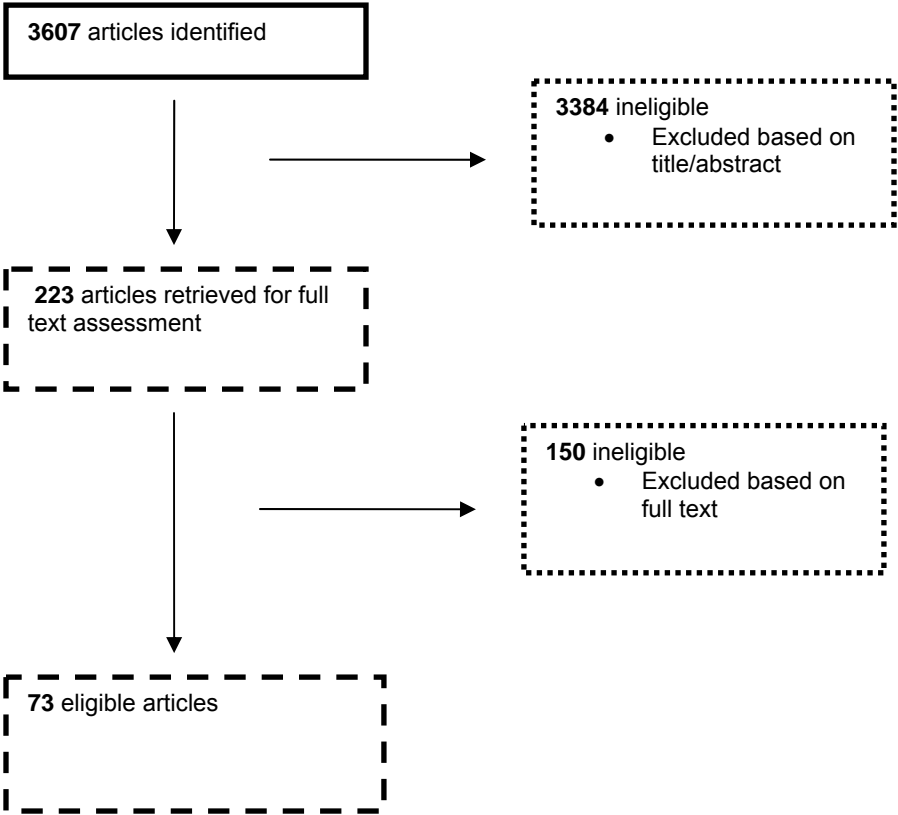
Country	Acronym	Organisation	Website
Australia	ACTR	Australian Clinical Trials Registry	http://www.actr.org.au/
	ANZBCTG	Australian New Zealand Breast Cancer Trials Group	http://www.anzbctg.org/
	NICT	National Institute of Clinical Trials	http://www.nhmrc.gov.au/nics/asp/index.asp?
Canada	CCO	Cancer Care Ontario	http://www.cancercare.on.ca/
International	HTAi	Health Technology Assessment International	http://www.htai.org/
	WHO	WHO International Clinical Trials Registry Platform	http://www.who.int/ictrp/en/
Scotland	SIGN	Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
United Kingdom	CCT	Current Controlled Trials	http://www.controlled-trials.com/
	NICE	National Institute for Health and Clinical Excellence	http://www.nice.org.uk/
	NRR	National Research Register	http://www.nrr.nhs.uk/
United States		ClinicalTrials.gov	http://www.clinicaltrials.gov/
	NCI	National Cancer Institute Clinical Trials	http://www.cancer.gov/clinicaltrials
	NGC	National Guideline Clearinghouse	http://www.guideline.gov/

Appendix 4 Terms used in search strategy

Key areas	Search Terms
Breast Cancer	(breast neoplasms/ or (breast and (cancer or carcinoma)))
Follow-up	“follow up care” or “follow up plan” or “follow up visit” or “follow up examination” or “clinical follow up” or “routine follow up” or “follow up model” or “follow up strategies” or “follow up methods” or “follow up program\$” or “routine test” or “postoperative surveillance” “post-treatment surveillance” or “post-therapy surveillance” or “breast cancer surveillance” or (surveillance and survivors) aftercare/ postoperative care/
Mammography	Mammography or mammography/ or “surveillance mammography”
Clinical breast examination	Clinical breast examination or physical examination or clinical examination
Breast self examination	Breast self examination or self breast examination

* / indicates Mesh terms, \$ indicates truncated terms.

Appendix 5 Flowchart of inclusion/exclusion process



Appendix 6 Summary of long-term side effects of treatments for breast cancer^{1, 80, 86}

MASTECTOMY, BREAST CONSERVING SURGERY, AXILLARY DISECTION

Psychosocial morbidity

- BCS & Mastectomy both have psychosocial morbidity, even 12 months after surgery

Problems with sexuality

- Following BCT or mastectomy, some women suffer problems with sexuality

Lymphoedema

- Both AD and AI, BCT and subsequent breast irradiation can lead to lymphoedema, and this can occur at any stage, even after years of treatment
- Patients with lymphoedema are at high risk of psychological distress

Chest wall discomfort & or breast pain

- Following mastectomy, axillary dissection, and breast conservation and subsequent breast irradiation - should settle within six months, however may last from three months to up to several years in some cases

A second primary tumour

- Can occur in retained breast tissue following breast reconstruction

Weakness of the abdominal wall

- Where tissue is in the rectus flap method of reconstruction following breast reconstruction

Frozen shoulder

- After either total mastectomy with axillary dissection or breast conservation with axillary dissection

RADIOTHERAPY

Tight skin

- Following radiotherapy

Abnormal sensation

- varying between discomfort and significant pain, particularly in the first two years.
- Sensory loss in the chest wall below or posterior to the axilla and in some cases on the medial and posterior aspect of the upper arm When axillary dissection has been performed

Breast-feeding

- is generally not possible in the irradiated breast, but cases where it has been possible have been reported

Brachial plexopathy

- Very rare - only occurs when the axilla and supraclavicular fossa are irradiated.

CHEMOTHERAPY

Alopecia

- Although hair usually grows back within three months of completing treatment, it may have a different texture and be curlier than before.

Sexual function and infertility

- associated with premature menopause. Sleep or appetite disturbances can also interfere with libido
- may significantly influence sexual functioning, body image and self-esteem in women
- 50–60 per cent of women treated for early breast cancer having sexual dysfunction beyond 12 months post-treatment.

Sense of impaired thinking and poor concentration

- There is limited research in this area.

Therapy-induced leukaemia

- Rare

Congestive cardiac failure

- Associated with higher cumulative doses of anthracyclines. It may be exacerbated by radiation therapy which includes the heart.

Febrile neutropenia

- Increased risk associated with taxane-containing regimens
- High risk associated with receiving a concurrent anthracycline and taxane-containing regimen managed with primary prophylaxis with growth factor support

TAMOXIFEN

Stroke, pulmonary embolism and deep vein thrombosis

- Elevated rates in women aged 50 years and over following treatment with tamoxifen
- Care should be exercised when tamoxifen is prescribed for patients taking warfarin as the metabolism of warfarin³⁴² is decreased, potentially leading to haemorrhagic complications.

Endometrial cancer

- Increased incidence in post-menopausal women.
- Women on tamoxifen therapy should be considered for annual gynaecological review.

Ovarian ablation

Premature menopause

- associated with significant vasomotor, sexual and other problems associated with oestrogen depletion, including increased risks of
 - osteoporosis and
 - Cardiovascular disease.

TRASTUZUMAB

Cardiotoxicity

- Longer term follow-up is needed to determine possible long-term cardiotoxicity associated with trastuzumab

Abbreviations

ACTR	Australian Clinical Trials Registry
AGO	Arbeitsgemeinschaft für Gynäkologische Onkologie
ASCO	American Society of Clinical Oncology
BC	Breast Cancer
BCT	Breast Conserving Therapy
BSE	Breast Self Examination
CBC	Contralateral Breast Cancer
CI	Confidence Interval
CT	Computed Tomography
CPG	Clinical Practice Guideline
DFS	Disease-Free Survival
EBC	Early Breast Cancer
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACT-B	Functional Assessment of Cancer Therapy-Breast
FACT-G	Functional Assessment of Cancer Therapy-General
GP	General Practitioner
HR	Hazard Ratio
NBCC	National Breast Cancer Centre
NBOCC	National Breast and Ovarian Cancer Centre
NCCN	National Cancer Control Network
NICE	National Institute for Health and Clinical Excellence
OR	Odds Ratio
OS	Overall Survival
PCP	Primary Care Provider
PET	Positron Emission Tomography
QoL	Quality of Life
RCT	Randomised Controlled Trial
SABCS	San Antonio Breast Cancer Symposium
SIGN	Scottish Intercollegiate Guidelines Network
UK	United Kingdom
US	United States
WHO	World Health Organisation

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